Diplomarbeit

BIOIMPEDANCE SPECTROSCOPY BEFORE AND AFTER ABDOMINAL PARACENTESIS: IMPLICATIONS FOR PERITONEAL DIALYSIS

zur Erlangung des akademischen Grades

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unter der Anleitung von

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Ort, Datum _____

Unterschrift (Studierender) _____

Eidesstattliche Erklärung

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Acknowledgment

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Secondly, I would like to thank the co-authors of the resulting paper for their thoughtful input and advice.

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Zusammenfassung

Hintergrund: Zur Bestimmung des Flüssigkeitsstatus von Peritonealdialyse (PD)-Patienten kann der Body Composition Monitor (BCM) unter Verwendung von Bioimpedanz-Spektroskopie eingesetzt werden. Eine Füllung des Peritonealraumes könnte die BCM-Messergebnisse verfälschen. Wir bestimmten deswegen Veränderungen in BCM-abgeleiteten Parametern nach abdomineller Parazentese und verglichen klinisch ermittelte Daten des Flüssigkeitsstatus mit den BCM-Messergebnissen.

Methoden: Entsprechend unserer vor Studienbeginn durchgeführten Fallzahlgrößen-Berechnung (Hauptparameter: Extrazelluläres Volumen [ECV], Nullhypothese: ECV Veränderung =1L von prä- zu post abdomineller Parazentese) führten wir 32 BCM-Messungen bei Patienten mit Leberzirrhose durch und erhoben demographische Werte sowie klinisch und laborchemisch relevante Parameter. Die statistische Methodik umfasste deskriptive Statistik, den 2-seitigen, gepaarten Student's T-Test und Pearsons Korrelationsanalyse.

Ergebnisse und Schlussfolgerungen: ECV, Gesamtkörperwasser und Fettgewebsmasse nahmen nach der Aszitespunktion signifikant ab. Die Korrelation der Werte von vor zu nach Aszitespunktion war nahe 1 für ECV aber nahe null für magere Gewebsmasse. Eine Korrelation zwischen dem klinisch ermittelten Flüssigkeitsstatus und der gemessenen Flüssigkeitsüberladung >15% ECV war nicht feststellbar. Wenn BCM-Messungen zur Evaluierung des Flüssigkeitsstatus bei PD-Patienten mit gefülltem Peritonealraum eingesetzt werden, sollte daher das Gewicht des PD-Dialysats von dem Körpergewicht eines Patienten abgezogen werden.

Abstract

Background: Bioimpedance spectroscopy using the body composition monitor (BCM) aids the evaluation of the fluid status in peritoneal dialysis (PD) patients. Filling of the peritoneal cavity might influence BCM results. We determined changes in BCM-derived parameters after abdominal paracentesis and compared clinical data of fluid overload with the BCM results.

Methods: Per our pre-specified sample size calculation (primary endpoint: extracellular volume [ECV]; null hypothesis: ECV change =1L pre to post-abdominal paracentesis), we performed BCM-measurements in 32 cirrhotic patients and also recorded demographics, laboratory values and clinical parameters. Statistical methods included basic descriptives, the 2-sided, paired Student's t-test and Pearson correlation analysis.

Results and Conclusions: From pre to post-ascites paracentesis, ECV, total body volume and adipose tissue mass decreased significantly. The correlation of the BCM-derived parameters from pre to post-ascites paracentesis was close to 1 for ECV but close to zero for lean tissue mass. We observed no correlation between the clinical assessment of the fluid status and fluid overload >15% ECV. When BCM measurements are performed in PD patients, the volume of the PD-fluid should therefore be subtracted from a patient's body weight when the BCM-measurement is performed with a full peritoneal cavity.

Introduction

In patients with end stage renal disease undergoing peritoneal dialysis (PD) or hemodialysis (HD), fluid overload (FO) identified by blood volume monitoring (Hussein, Arramreddy, Sun, Doss-McQuitty, & Schiller, 2016; Rodriguez, Domenici, Diroll, & Goykhmann, 2005; Sinha, Light, & Agarwal, 2010) or whole body bioimpedance spectroscopy (BIS) (Chamney, Krämer, Rode, Kleinekofort, & Wizemann, 2002; Kraemer, Rode, & Wizemann, 2006; Passauer, Petrov, Schleser, Leicht, & Pucalka, 2010; Wizemann et al., 2009) is associated with increased mortality (Agarwal, 2010; Ateş et al., 2001; Chazot et al., 2012; Drepper et al., 2016; Hecking et al., 2013; Oei et al., 2016; Paniagua et al., 2010; Wizemann et al., 2009). Unlike blood volume monitoring (Hecking & Schneditz, 2017), which is restricted to HD patients, BIS provides information on quantitative tissue distribution as well as fluid distribution in the extracellular and intracellular body compartments and can be used in HD as well as in PD.

In dialysis patients, studies hint at a survival advantage associated with obesity (reverse epidemiology) (Hecking et al., 2014; Kalantar-Zadeh, Abbott, Salahudeen, Kilpatrick, & Horwich, 2005). Multiple studies have shown a significant correlation between decreased fat or muscle mass and increased mortality (Kalantar-Zadeh et al., 2012; Marcelli et al., 2015; Tapolyai et al., 2011;

Wizemann et al., 2009). This correlation contributes to the challenge of evaluating 'dry weight' clinically: In general the clinical assessment of FO is often difficult and susceptible to errors. Besides the clinical exam, practitioners can assess interdialytical weight gain (IDWG), defined as weight gain in two constitutive dialysis sessions or body mass index (BMI) calculated by dividing body weight by the square of height. They are simple methods and can be easily performed in the clinical setting. Yet, both IDWG and BMI cannot discriminate between changes in fat mass, muscle mass or FO. So they can only depict, not explain, weight changes. For IDWG, studies show that only a high increase in IDWG is patients with moderate increase in IDWG, fat mass and lean mass should be evaluated to determine the likeliness of FO, because patients with low IDWG and high FO have the highest mortality risk (Hecking et al., 2018). As IDWG cannot effectively predict FO on its own, it has been postulated to replace IDWG by FO as a surrogate marker (Hecking et al., 2013). With respect to BMI, several previous studies have observed an inverse correlation between body mass index and FO in dialysis patients (Antlanger et al., 2013; Biesen et al., 2011; Ribitsch, Stockinger, & Schneditz, 2012). Yet, the findings on the consequence of fat mass on mortality in HD patients are conflicting (Park et al., 2014). If no BCM-BIS device is at hand, use of serum creatinine level as a marker of muscle mass is helpful as it seems to predict mortality better than BMI (Kalantar-Zadeh et al., 2012; Sakao et al., 2016). Thus, periodic evaluation of muscle mass, fat mass and fluid distribution is helpful in treating PD patients, not only for target weight

assessment but also to monitor body composition and changes in body composition.

The Body Composition Monitor (BCM) applies whole-body BIS to measure FO, assess muscle mass, fat mass and fluid distribution in general. The benefit of using BCM-BIS to evaluate 'dry weight' (Jaeger & Mehta, 1999; Wystrychowski & Levin, 2007) has been recognized for HD patients (Chamney et al., 2002; Machek, Jirka, Moissl, Chamney, & Wabel, 2010; Onofriescu et al., 2014), and more recently for PD patients (Oei et al., 2016), while prospective studies aiming at determining hard outcomes in PD patients using BCM-BIS are ongoing (Baek et al., 2014; Su et al., 2011).

Filling of the peritoneal cavity occurs not only in patients undergoing PD, but also in cirrhotic patients with portal hypertension, who develop ascites (Bucsics et al., n.d.; Reiberger et al., 2017) Both patient groups may undergo large and relatively quick fluctuations of the so called 'third space'. Possible effects of the filling of the peritoneal cavity on BIS results are subject of ongoing discussions (Arroyo et al., 2015; Parmentier et al., 2013; Sipahi et al., 2011). The disunity is mirrored by different filling status throughout various studies using BIS: some researchers measure with a full abdomen (Davison, Jhangri, Jindal, & Pannu, 2009; Devolder, Verleysen, Vijt, Vanholder, & Biesen, 2010;

Ventura Aguiar et al., 2015), others after the abdomen was drained (Abad et al., 2011; Cooper et al., 2000; Luo, Lu, Woods, & Wang, 2011; Yılmaz et al., 2014), or do not elaborate on the matter, assuming there is no difference (Biesen et al., 2011; Lee et al., 2006).

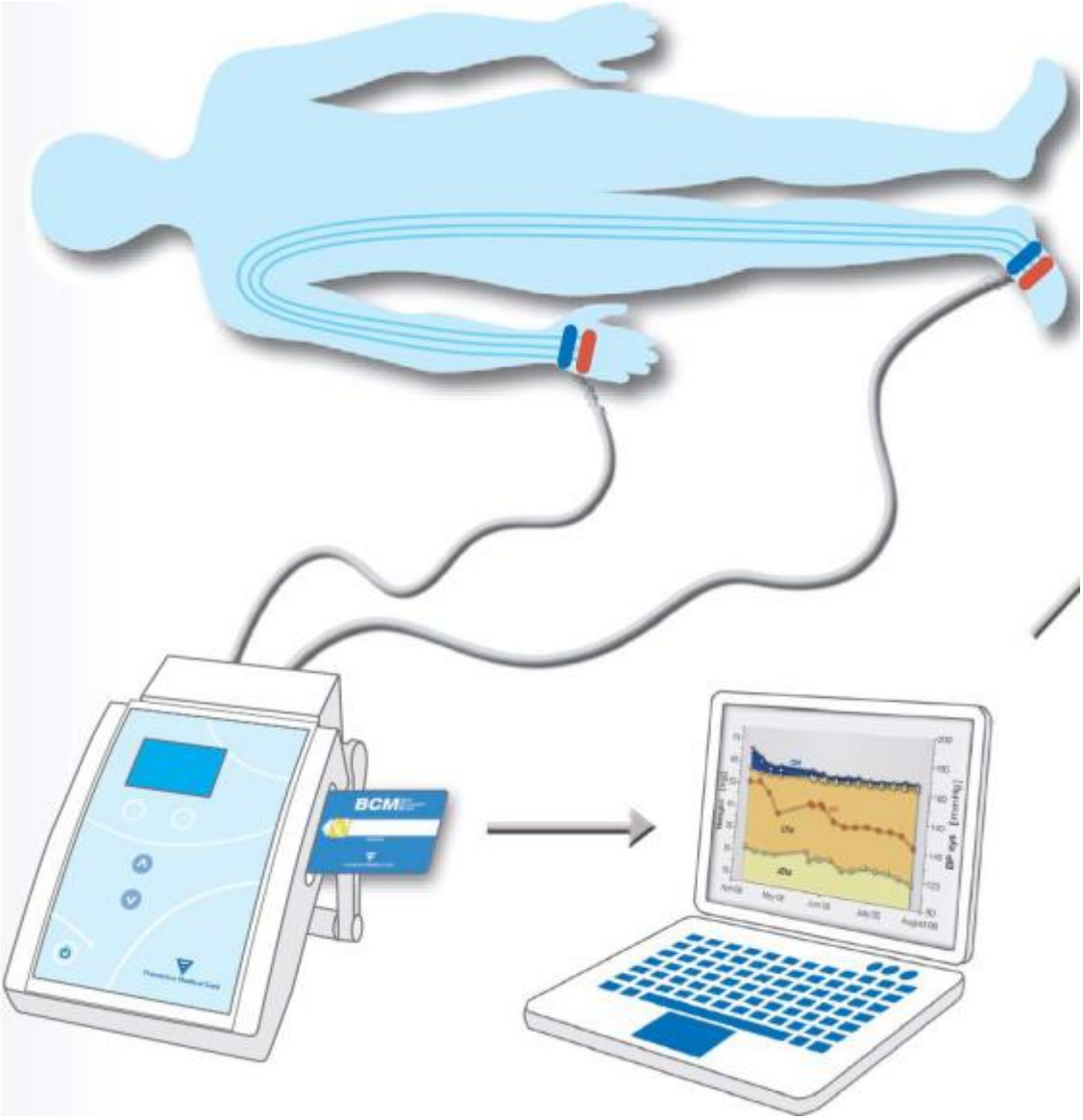
The aim of the present study was to assess changes in BCM-derived parameters from before to after abdominal paracentesis, in order to evaluate whether the filling status of the peritoneal cavity influences the BCM results. As a secondary goal, we also compared clinical signs of FO with results of BCM-BIS.

Methods

Body Composition Monitor

BIS using the BCM is a non-invasive technique (Ernstbrunner et al., 2017). In the present study, we conducted all BCM measurements in accordance with the manufacturer's instruction (Fresenius Medical Care, Bad Homburg, Germany): After the patient had rested for at least 5 minutes in supine position, 2 non-recyclable electrodes were affixed to wrist and ankle, respectively. The BCM electrodes were connected with a cable, provided by the manufacturer (see image 1). Basic demographic data of the patient (sex, age, height, weight) were entered into the BCM-device.

Image 1: Body Composition Monitor



The picture schematically depicts a BCM-measurement: First, practitioners enter basic demographic data (sex, age, height, weight) of the patient into the BCM device. Then 2 electrodes are affixed to wrist and ankle, respectively, between which current passes through the body. The BCM is connected with the electrodes via two cables attached to the electrodes. The subsequent BCM

calculation takes around two minutes. It is possible to transfer the results of the measurement to a computer to keep track of changes in BCM measurement in patients repetitively measured. (Fresenius, n.d.)

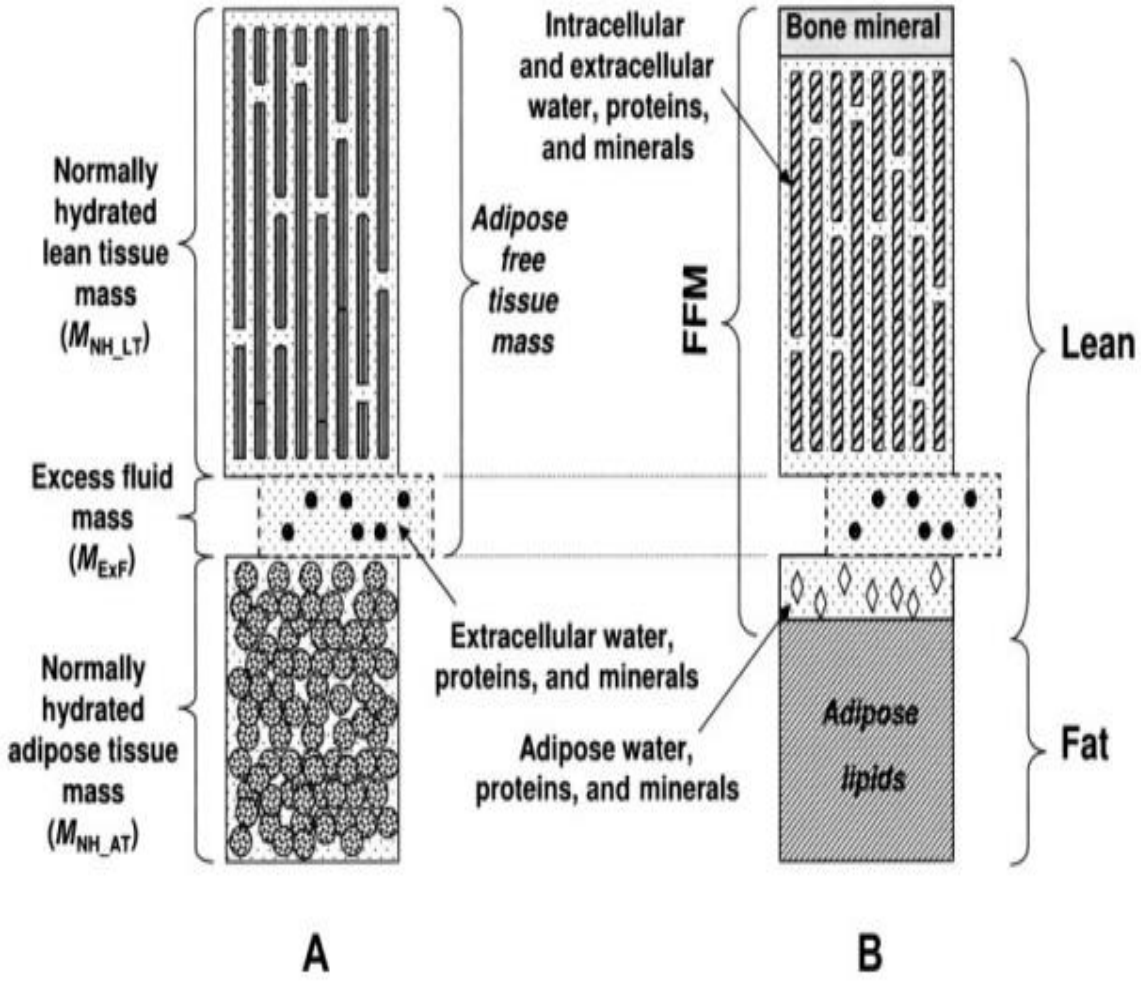
The BCM device generates resistance and reactance values at 50 distinctive frequencies in the range of 5 to 1000 kHz. The mathematical algorithm of the BCM device then calculates within normally less than 2 minutes absolute values of tissue and fluid distribution on the basis of 3 models: firstly, resistance values for extracellular volume (ECV) and intracellular volume (ICV) are calculated by referring to a Cole Model (Cole, Li, & Bak, 1969). Secondly, these resistance values are transformed into ECV, ICV and total body volume (TBV) values employing a model by Moissl (Moissl et al., 2006). The whole body model by Chamney (Chamney et al., 2007) then distinguishes FO from physiologically hydrated adipose and lean tissue mass, the last 2 being characterized by invariable coefficients of fluids (see image 2).

Per the BCM algorithm, measured individuals are compared to a healthy collective with the same body weight. Measured values of ECV and its proportion to physiological ECV values of the healthy comparison group provide the basis for the calculation of excess fluid and absolute values for tissue distribution. The difference between measured and physiological ECV is defined as fluid excess (FO). The BCM device finally also provides all results for fluid excess in liters and in % of ECV (Chamney et al., 2007b).

A general note: In accordance with other authors (Ernstbrunner et al., 2014), we did not adopt the nomenclature included in the BCM-device (i.e. of

‘overhydration’ and ‘extracellular water’). Although overhydration, FO and volume overload are often used synonymously, ‘hydration’ strictly refers to water whereas ‘volume expansion’ describes the accumulation of isotonic fluid (salt and water). We therefore replaced the term overhydration by ‘FO’ and coherently replaced the terms extracellular water, total body water and intracellular water by ECV, TBV and ICV (using volume [V] instead of water).

Image 2: Whole Body Model by Chamney



A: The new 3-compartment model comprising normally hydrated adipose tissue mass (MNH_AT), normally hydrated lean tissue mass (MNH_LT), and excess fluid mass (MExF).

B: Relation between the compartments of the new model and standard measures of body composition in terms of lean mass, fat mass, and fat-free mass (FFM).

(Chamney et al., 2007a, p. 82)

Study details

BCM-measurements were implemented into routine clinical practice of the Department of Gastroenterology and Hepatology on 1-June-2016. From that day onward until 1-July-2017, patients with ascites caused by liver cirrhosis, identified through the ward and the outpatient clinic were measured by BCM and carefully examined. BCM measurements were undertaken before and after abdominal paracentesis by 2 independent investigators (Amrei Simon, Manfred Hecking). In case of insufficient quality of measurements (quality of data below 70%), the measurement was repeated. Because the BCM device always calculates the fluid status on the basis of body weight, the patient's body weight has to be entered into the device at every measurement. The body weight of the second measurement was obtained by subtracting the ascites volume from the initial weight under the presupposition that 1L of withdrawn ascites volume equals 1kg of body weight. Clinical signs of FO (peripheral edema) were evaluated before the first measurement, and so were heart frequency and blood pressure.

In accordance to our ethic commission proposal (EK#2096/2016), we recorded demographic data that included patient age, height, body weight, body mass index and etiology of liver cirrhosis. We additionally recorded whether a patient was treated with diuretic agents. To assess kidney and liver function, we

obtained the following laboratory parameters: serum albumin, alanine aminotransferase, aspertate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, bilirubin, international normalized ratio, serum creatinine, blood urea nitrogen, blood urea nitrogen/serum creatinine, serum potassium and serum sodium concentration. Child-Pugh-Score was calculated on the basis of serum albumin, bilirubin, international normalized ratio, sonographic evaluation of ascites and symptoms of hepatic encephalopathy.

We registered the time between the BCM measurements, the volume of the abdominal paracentesis, all BCM-derived values and the volume of the albumin infusion administered after abdominal paracentesis. According to current guidelines, patients received 8g of human albumin per liter of ascites fluid removed, using a 20% formulation (manufactured by CSL Behring GmbH) containing at least 19.2g albumin per 100mL infusion solution.

Sample size calculation and statistical methods

The primary endpoint was defined, per our pre-specified study protocol, as the difference (delta) of measured ECV in patients from before to after abdominal paracentesis. Secondary endpoints included the deltas of measured TBV and ICV in patients from before to after abdominal paracentesis and also included the correlation between clinical signs of FO and a BCM-derived classification

of FO (>15% ECV).

The pre-specified sample size calculation was based on Student's t-test for dependent samples. In our previous study (Ernstbrunner et al., 2014) the standard deviation of the ECV values in patients receiving perioperative fluid therapy was approximately 2L. Using this standard deviation and assuming a moderate and thereby clinically meaningful within-subject correlation (r) of 0.5 and a beta value of 0.2, we arrived at the conclusion that 31 subjects would be needed to determine an effect size of 1L (delta ECV from before to after abdominal paracentesis) at a statistical significance level of 0.05.

Descriptive statistics (mean and standard-deviation for normally distributed variables) were employed to depict patients' characteristics, laboratory values and BCM-derived results. All deltas of the BCM measurement were evaluated using the 2-sided, paired Student's t-test and Pearson's correlation analysis.

A patient was considered to be fluid overloaded, when FO/ECV*100 exceeded 15%. We then used Fisher's exact test to analyze the association between clinical signs of FO (classified categorically by the presence of edema) and BCM-derived FO (>15% ECV), between the clinical signs of FO (edema) and diuretic therapy and between BCM-derived FO (>15% ECV) and diuretic therapy.

For calculations we used MS Excel 2007 (Microsoft corporation®, Redmond, Washington, USA) and IBM SPSS Statistics 22.0. (IBM SPSS 22.0, IBM corporation®, Armonk, NY, USA). P-values <0.05 were considered statistically significant.

Results

Characteristics of the study population

26 of 32 patients were male and mean age of the cohort was 59.2±11.1 years (on average±standard deviation, Table 1). Mean weight of the cohort was 79.8±16kg, mean height was 175.8±11.2cm and mean body mass index was 25.9±4.7kg/m^2. The documented etiology of the liver cirrhosis causing ascites was as follows: 14 patients suffered from alcohol-induced liver cirrhosis, 7 patients from viral hepatitis, 3 patients from liver cirrhosis of unknown origin, 2 patients from hepatocellular carcinoma, while 1 patient had an autoimmune hepatitis causing liver cirrhosis, 1 patient had Wilson's disease, 1 patient had duodenal carcinoma with metastasis of the liver, 1 patient had polycythemia vera, 1 patient had primary sclerosing cholangitis and 1 patient had non-alcoholic steatohepatitis. 31 patients had Child-Pugh Score >A, the Child-Pugh Score of the only remaining patient of the outward clinic could not be assessed (laboratory values not documented).

Mean serum creatinine of the study cohort was 1.5±1.0mg/dL in the male group and 0.9±0.4mg/dL in the female group. Mean creatinine was elevated above the normal range (shown in Table 1) in 13 men whose mean creatinine was 3.0±1.8mg/dL and in 3 women whose mean creatinine was 1.2±0.3mg/dL.

Mean blood urea nitrogen of the study cohort was 33.9±29.0mg/dL and was below the normal range in 7 patients whose mean blood urea nitrogen was 6.6±0.6mg/dL and was elevated above the normal range in 14 patients whose mean blood urea nitrogen was 57.3±27.2mg/dL. Mean serum sodium was 134.0±6.2mEq/L. 17 patients had hyponatremia below 135mEq/L, but were neurologically asymptomatic; their mean serum sodium levels were 129.4±4.7mEq/L.

20 patients were using diuretics at the time of the measurement. In 27, respectively 18 patients, heart rate and blood pressure values were within the normal range (81.7±9.7 beats/minute for heart rate, 107.0±8.0mmHg for systolic blood pressure and 69.6±6.4mmHg for diastolic blood pressure, respectively; normal ranges shown in Table 1). 20 patients had edema. The mean volume of the abdominal paracentesis was 7.7±2.6L, mean duration of the procedure was 125.3±41.5 minutes. Mean volume of albumin infusion of a 20% formulation was 293.8±107.6mL.

Table 1: Demographic data and clinical characteristics of the study population

	All	Normal range
Number of patients	32	
Age [years]	59.2±11.1	
Male sex [percentage of total number of patients]	81.3%	
Height [cm]	175.8 ±11.2	
Weight [kg]	79.8±16	
Body mass index [kg/m²]	25.9±4.7	
„Dry weight“ [kg]	76.5±15.1	
Child Pugh Score >A	31	
Number of patients with diuretics	20	
Serum albumin [g/L]	30.4±5.4	35-52
Alanine aminotransferase [U/L]	71.5±151.5	12-46
Aspartate aminotransferase [U/L]	106.5±143.1	10-55
Alkaline phosphatase [U/L]	117.2±156.8 (male) 61.5±43.5 (female)	40–130 (male) 35-105 (female)
Gamma-glutamyltransferase [U/L]	241±242.1 (male) 57.3±54.7 (female)	60 (male) 40 (female)
Bilirubin [mg/dL]	4.7±7.1	0.3-1
International Normalized Ratio	1.5±0.3	
Serum creatinine [mg/dL]	1.5±1.0 (male) 0.9±0.4 (female)	0.70-1.20 (male) 0.50-0.90 (female)
Blood urea nitrogen [mg/dL]	33.9±29.0	8-23
Blood urea nitrogen/serum creatinine	22.3±13.7	
Serum sodium [mEq/L]	134.0±6.2	136-145
Serum potassium [mmol/L]	4.4±0.8	3.5-5.1
Systolic blood pressure [mmHg]	112.6±14.4	90-120

Diastolic blood pressure [mmHg]	67.7±8.6	60-80
Heart rate [min $^{-1}$]	85.2±12.2	60-100
Edema	20	
Volume of abdominal paracentesis [L]	7.7±2.6	
Duration of abdominal paracentesis [min]	125.3±41.5	
Infusion volume of human albumin Kedrion 200g/L [mL]	293.8±107.6	

All continuous parameters are presented as means ± standard deviations.

Normal range of laboratory values is given when considered reasonable.

BCM-derived fluid status and body composition before and after abdominal paracentesis

The following significant changes were noted for BCM-derived parameters from before to after abdominal paracentesis (on average±standard deviation, Table 2): ECV decreased (from 19.9±4.9L to 18.8±4.6L, $p<0.001$), TBV decreased (from 39.8±10.2L to 37.9±8.7L, $p=0.01$), adipose tissue mass (ATM) decreased (from 39.7±16.0kg to 30±12.9kg, $p<0.001$), fat mass decreased (from 28.4±11kg to 22.3±9.5kg, $p<0.001$) and fat mass percentage decreased (from 35±10.5% to 30.2±9.5%, $p=0.01$) while lean tissue mass percentage increased (from 47.5±13.4% to 53.6±13%, $p=0.01$).

The correlation of BCM-derived fluid parameters from before to after abdominal paracentesis (Figure 1) was smallest for FO ($R^2=0.51$, Figure 1A), followed by TBV ($R^2=0.85$, Figure 1B) and followed by ICV ($R^2=0.57$, Figure 1D), while the correlation was greatest for ECV ($R^2=0.99$, Figure 1C). The correlation of BCM-derived parameters of the body composition from before to after abdominal paracentesis (Figure 2) was null for lean tissue mass ($R^2=0.03$, Figure 2A) and weak for fat mass ($R^2=0.11$, Figure 2B) as well as for ATM ($R^2=0.11$, Figure 2C).

Table 2: Results of Body composition monitor (BCM)-measurements before and after abdominal paracentesis

	Results before paracentesis	Results after paracentesis	Mean patient difference	p-value
Fluid overload	3.25±2.44L	3.25±2.72L	-0.02L	0.77
Fluid overload percentage	15.3±10.1%	17.6±13.1%	2.3%	0.39
TBV	39.8±10.2L	37.9±8.7L	-2.2L	0.01
ECV	19.9±4.9L	18.8±4.6L	-1.0L	<0.001
ICV	19.9±6L	19.1±4.9L	-1.3L	0.16
ECV/ICV	1.0±0.2	1.0±0.2	0.0	0.64
Adipose tissue mass	39.7±16.0kg	30±12.9kg	-10.5kg	<0.001
Lean tissue mass	38.2±12.8kg	38.5±10.7kg	1.2kg	0.92
Lean tissue mass percentage	47.5±13.4%	53.7±13%	6.5%	0.01
Fat mass	28.4±11kg	22.3±9.5kg	-5.9kg	<0.001
Fat mass percentage	35±10.5%	30.2±9.5%	-5%	0.01
Fat Tissue Index	12.6 ± 5.2 kg	10.4 ± 4.3 kg	-2.3 kg	<0.001
BCM	20.1 ± 8.6 kg	20.4 ± 7.3 kg	0.2 kg	0.91

Harnstoff	37.5 ± 10.0 L	34.8 ± 8.9 L	-2.7 L	0.26
NH-Gewicht	76.5 ± 15.1 kg	67.9 ± 15.2 kg	-8.6 kg	0.03

All variables in the second and third vertical column are means ± standard deviations. Values in the fourth column were derived by averaging the results of the formula: BCM result after abdominal paracentesis - BCM result before abdominal paracentesis.

[a] TBV = total body volume, ECV = extracellular volume, ICV = intracellular volume, ECV/ICV: Quotient of extracellular volume and intracellular volume.

Figure 1: Scatterplot of different body fluids with full (x-coordinate) and empty (y-coordinate) peritoneal cavity

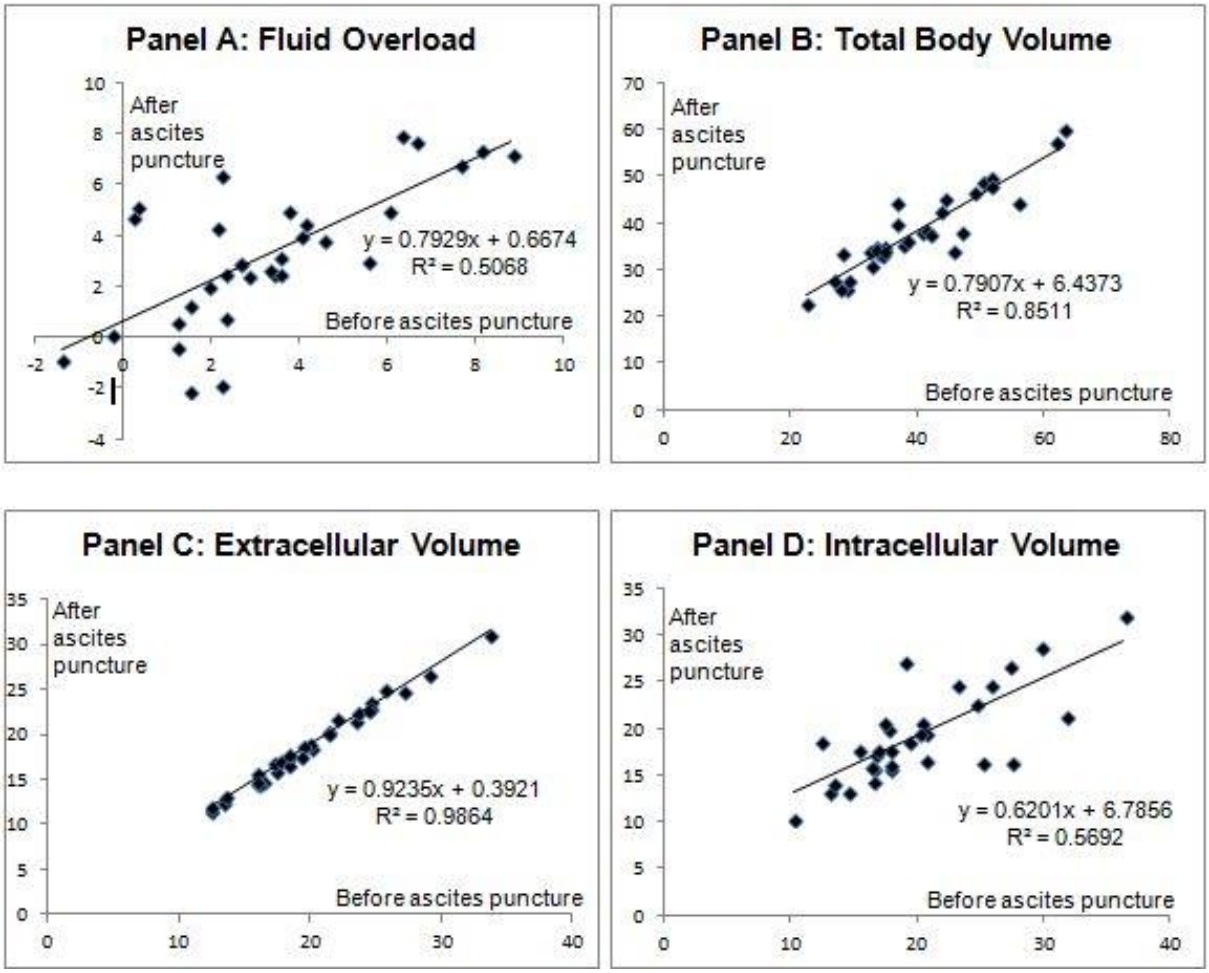
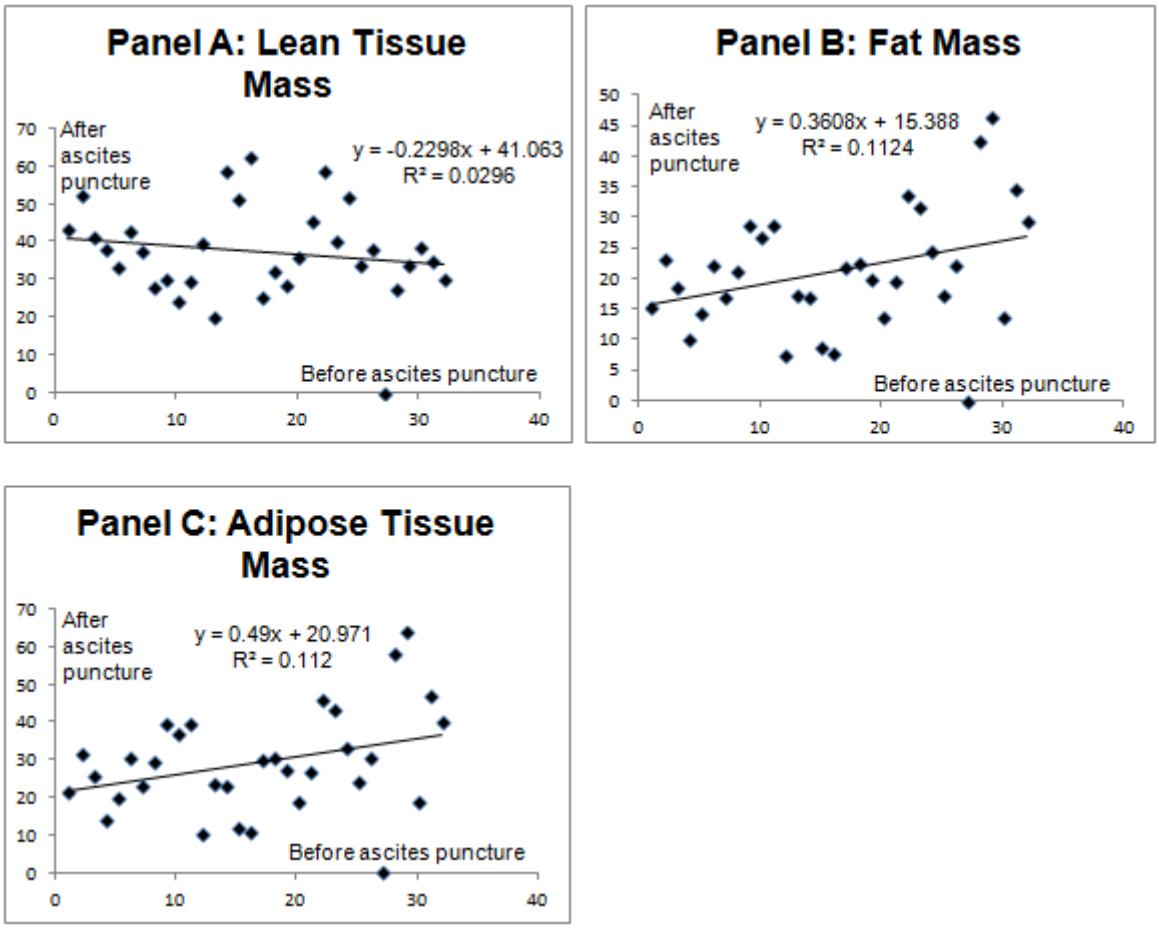


Figure 2: Scatterplot of different body compartments with full (x-coordinate) and empty (y-coordinate) peritoneal cavity



Correlation between BCM-derived FO and clinical symptoms

The clinical fluid status of the study patients, evaluated before the BCM measurement did not correlate with the presence of BCM-derived FO prior to the abdominal paracentesis (Table 3). Specifically, among 20 patients who had edema, 16 patients had BCM-derived FO >15% ECV (p=0.27, Table 3). This result was similar after the abdominal paracentesis, where among 20 patients who were classified as having edema, 21 patients had BCM-derived FO >15% ECV (p=0.25). Similarly, we did not observe any correlation between BCM-derived FO and the treatment with diuretics, either before or after the abdominal paracentesis (p=0.29 and p=0.70, respectively). Finally, we did not observe a significant correlation between the use of diuretics and clinical signs of FO (p=0.72).

Table 3: Correlation between clinical findings and between clinical findings and BCM-results

	Parameter 1	**Parameter 2**	**p-value**
Before abdominal paracentesis	Edema (20 patients)	Fluid overload >15% ECV (16 patients)	0.27
After abdominal paracentesis	Edema (20 patients)	Fluid overload >15% ECV (21 patients)	0.25
Before abdominal paracentesis	Diuretic therapy (20 patients)	Fluid overload >15% ECV (16 patients)	0.29
After abdominal paracentesis	Diuretic therapy (20 patients)	Fluid overload >15% ECV (21 patients)	0.70
	Edema (20 patients)	Diuretic therapy (20 patients)	0.72

Fluid overload was defined as fluid overload/ECV*100 >15%. Diuretic therapy was defined as at least 1 diuretic drug at the time of measurement.

Discussion

The present study shows that the removal of ascites from the peritoneal cavity significantly influences the fluid results obtained by bioimpedance spectroscopy using the BCM device. The large changes in BCM-derived fat mass from before to after abdominal paracentesis are not physiologically plausible and imply that the fat compartment is overestimated by the BCM device in patients who have large fluid volumes contained within the peritoneal cavity. Thirdly, the results of clinical assessment of FO differed significantly from the results of the BCM device.

Among all BCM-derived parameters, ECV as well as FO in the extracellular compartment are of primary clinical importance to nephrologists. The fact that the present study identified a significant decrease in ECV from before to after the abdominal paracentesis could have implications for the use of the BCM device in patients with peritoneal filling: If the BCM device might measure ECV incorrectly in such a collective, clinicians would obtain erroneous values of FO and thus potentially mistreat patients with moderate peritoneal filling, such as PD patients. However, a withdrawal of a large ascites volume causes pressure dynamics to change. A change in pressure dynamics might cause abdominal edema to vanish and fluid to flow back into the peritoneal cavity

(Shear, Ching, & Gabuzda, 1970). Furthermore we observed a high correlation of ECV between measurements (R^2=0.99), which implies that ECV is largely independent of the peritoneal filling. Although ECV changed significantly, the mean patient difference of ECV with peritoneal filling and ECV after abdominal paracentesis was only slightly above our threshold of 1.0L (1.029L). In view of these considerations, we consider the decrease of ECV in our patient collective to be more likely caused by physiologic changes due to the abdominal paracentesis itself rather than a default in the BCM device.

Only few studies have evaluated the effect of peritoneal filling on ECV values measured by the BCM device, and the findings of these studies are diverse: Arroyo et al. found significant changes in EZV, FO and FO/ECV but no significant changes in body compartment parameters and TBV or ICV. They filled the peritoneal cavity with 2 liters of 1.36% glucoses, measuring the patient before application and after the filling was drained. The time between measurements was up to two hours (Arroyo et al., 2015). In Arroyo's study other factors might have caused an overestimation of ECV (order of measurements, time between tests, amount of ultrafiltration or testing before the beginning of the dwell) (Minguela, Jimeno, Aurrekoetxea, & Ruiz de Gauna, 2015). Sipahi et al. demonstrated a higher conformity of BCM results with echographic findings of left ventricular mass and left atrium volume in measurements with an empty peritoneal cavity, without any significant changes

in BCM-derived parameters (Sipahi et al., 2011). Finally, Parmentier et al. did not register any significant changes in ECV, comparing BCM results of PD patients under PD treatment therefore conducting 42 measurements at total (one with full abdomen, one with empty abdomen) in 17 patients. Parmentier did not elaborate explicitly on the amount of peritoneal filling (change of weight between measurements was about 1.7kg) or on the time gap between the administration of dialysate and BCM measurements (time gap between measurements was 45 minutes maximum) (Parmentier et al., 2013) - both factors that have consequences on pressure dynamics, shift of fluids and, thus, ECV. So before the first measurement with full abdomen, ECV might have changed unnoted to Parmentier or the residual volume left in the peritoneal cavity was too small at the time of measurement to have an effect on pressure dynamics.

Strictly speaking, further studies should be conducted to scrutinize how a filling of the peritoneal cavity changes ECV. However, the data of the present study that made use of large ascites volumes removed from the peritoneal cavity in patients with liver cirrhosis and observed a decrease in ECV after ascites removal are in accordance with the results of Arroyo et al. who noted an increase after filling of the peritoneal cavity.

We observed a significant change in ATM, lean tissue mass percentage and fat mass, which, unlike the significant change of ECV, cannot be explained by physiological changes between the BCM measurements. Undoubtedly, the BCM device is susceptible to erroneously attributing the weight of the ascites volume to the fat compartment. Specifically, the abdominal paracentesis led to 2 different body weights of the same patients in our study: the first body weight before the paracentesis (which includes the entire ascites) and the second body weight after the paracentesis (where we subtracted the mass of the ascites fluid from the initial body weight). The erroneous differences in ATM, lean tissue mass percentage and fat mass are likely due to the fact that the BCM device does not recognize the ascites fluid (the current passes through).

As ICV, ECV, lean tissue mass and ATM sum up to a patient's body weight, a change in body weight due to ascites removal causes a wrongful attribution of ascites mass to one of the summands. FO is mainly dependent on ECV which itself is independent of body weight. Lean tissue mass did not shift significantly, yet there was hardly any correlation (R^2=0.03) between pre- to post-values. ATM changed significantly and with it fat mass. In clinical practice it therefore seems to be necessary to either clear the peritoneal cavity from fluid or to subtract the mass of the fluid within the peritoneal cavity from a patient's body weight in order to obtain correct values of tissue distribution.

Another explanation for the change of tissue parameters is given by Davenport et al. who have recently shown that FO itself can lead to an overestimation of ATM and underestimation of lean tissue mass in hemodialysis patients (El-Kateb & Davenport, 2016). Both in pre- as well as post-paracentesis measurements, 16 respectively 21 patients had a mean FO/ECV ratio of more than 15 % contributing to an overall FO/ECV ratio of more than 15 % (15.3% on average±10.1% standard deviation and 15.8% on average±12.8% standard deviation respectively). It will be important to scrutinize the impact of changes in body weight and FO on the accuracy of BCM results, as lean tissue mass and ATM are important clinical parameters for morbidity and mortality of patients undergoing dialysis.

In our study FO did not change significantly, although ECV did. FO is derived by the BCM device by associating the measured ECV with an expected ECV obtained by a collective of the same body weight. Thus, a falsified weight, generated by a filling of the peritoneal cavity, might cause false values of FO. Furthermore lean tissue mass and ATM have different coefficients of fluid (ECV) in the whole body model. An overestimation of either lean tissue mass or ATM changes the volume of ‘free’ ECV. In this theoretical sense, an overestimation of lean tissue mass or ATM might distort FO results. In theory,

these 2 factors (falsified body weight and overestimation of ATM or lean tissue mass) combined could disguise significant changes of FO. It is more likely though, that the falsified body weight leads to marginal change in FO. Parmentier et al. for example did not find significant changes in fluid overload at different filling status with adopting body weight to the moderately filled peritoneal cavity (Parmentier et al., 2013). Further studies should be conducted in order to justify the use of FO (OH) as a surrogate parameter, rather than using ECV which in our study had a higher correlation between measurements.

Interestingly, we could not identify a significant correlation between FO and the use of diuretics or clinical assessment of FO (edema) in our study patients. Our findings are in line with Ronco et al. (Ronco et al., 2015) who also observed a discrepancy between the clinical assessment of fluid status and BCM-derived evaluation of fluid status, and identified the highest predictive value in fluid overloaded PD patients. Due to our limited sample size it remains open to discussion whether Ronco et al.'s results might have been reproduced in liver cirrhosis patients. The volume status of a cirrhotic patient is difficult to evaluate and clinical signs of FO in this patient collective can be misleading. BCM-derived parameters could provide important information on volume status of these patients in the future, especially as the use of diuretics in patients with liver cirrhosis has to be cautiously introduced since both oversubscription

and undersubscription have serious side effects (Ginès, Cárdenas, Arroyo, & Rodés, 2004).

The absence of a correlation between clinical signs of fluid overload and diuretics could be explained by patients' characteristics that may lead to an end of diuretic therapy in patients with clinical signs of fluid overload (such as kidney dysfunction or a weight loss of more 800-1000 mg per day under diuretic therapy or serum sodium decreases to less than 120–125 mmol/L) (European Association for the Study of the Liver, 2010; Ginès et al., 2004). Additional volume status of patients with liver cirrhosis is hard to evaluate clinically and absence of edema does not imply absence of fluid overload.

The strength of this study is firstly the simulation of volume shifts during PD by abdominal paracentesis, which enables to depict how an immense filling of the peritoneal cavity with osmotic largely ineffective volume has significant impact on ECV and that adopting body weight to the filling status of the cavity impacts BCM results of the body compartments. Secondly, our study has implications for 2 different areas of medicine, namely hepatology and nephrology: the demonstrated disparity between clinical assessment of FO and BCM-derived FO needs further evaluation both in reference to PD patients and the use of BIS device in liver cirrhosis patients.

The study had several limitations: First, to our knowledge BCM has not been tested in patients with liver cirrhosis and error might arise from comparing liver cirrhosis patients with a healthy patient collective. Second, as our study is to our knowledge the first of its kind, comparable data could not be obtained. Third, the few studies scrutinizing the same endpoints in question were difficult to compare to each other and to our study. Fourth, our patients have a greater filling of the peritoneal cavity than PD patients, making it necessary to conduct a comparable study with PD patients to further evaluate the consequence of peritoneal filling on the BCM device.

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List of used abbreviations

ATM	Adipose tissue mass
BCM	Body Composition Monitor
BIS	Bioimpedance spectroscopy
BMI	Body mass index
ECV	Extracellular volume
FO	Fluid overload
HD	Hemodialysis
ICV	Intracellular volume
IDWG	Interdialytical weight gain
PD	Peritoneal dialysis
TBV	Total body volume